Aluminum Phosphide Poisoning in Animals

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Several articles have showed the effect of ALP toxicity on different organs. Toxicity mechanisms are not clearly understood yet. Due to the potential increased use of ALP as a fumigant and the lack of adequate toxicity data, previous studies were re-evaluated to characterize the epidemiological, toxicological, and clinical/ pathological aspects of ALP poisoning and its management. Related terms were looked up in bibliographical databases such as the Tehran University Medical Science Digital Library, PubMed, Scopus, Google Scholar, and British library. The studies suggest that phosphine targets the mitochondria and inhibits respiration in rat liver mitochondria, insect mitochondria, and intact nematodes. On the other hand, glutathione (GSH) levels are reduced in various tissues of ALP-poisoned rats, while remaining unchanged in insects and mammalian cells. Also, acetylcholine signaling is an important component of phosphine toxicity. Phosphine (PH_3) induces oxidative stress and lipid peroxidation in insects, mammalian cells, and other animals. There is no known antidote for ALP intoxication; but, melatonin as an effective antidote protects against oxidative damage in the brain, lung, and liver of the rats and suggests the involvement of ROS in the genotoxicity of PH_3. Cholinesterase inhibition responds to treatment with atropine, pralidoxime, and oral sweet almond oil, especially if used immediately after ALP poisoning. Several treatments have been used in animals some of which have not been tested in human-beings yet. Such treatments should be given in controlled situations with the hope they may be helpful in treating these patients.

►*Implication for health policy/practice/research/medical education:* Aluminum Phosphide Poisoning

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1. Introduction:

Providing food has always been a challenge to human; the only major cornerstone in this challenge is the competition with pests (1). Different kinds of pests including animals and insects are the major problem in agriculture, hygiene, and industry (2). It is difficult to quantify the exact cost of damage caused by the pests. The most effective way for controlling pest damage depends on the situation and temperament of the people involved (3). Nonchemical ways are attractive because they neither leave chemical residues in the commodity nor do they cause resistance in pests (1). Fumigation plays a key role in control and management of infestation stored commodities worldwide (4-7).

Aluminum phosphide (ALP) (also known as rice tablet in Iran) is the most commonly used solid fumigant in our country (8-10) which protects stored grains (4, 10-13). Its application is rapidly increasing due to its wide availability, high efficacy against different pests, lack of persistence, low cost, and safe decomposition products that are considered to be environmentally safe (12, 14-16). On the other hand, it is proved that ALP is toxic to both human beings and animals (14, 16-21). The toxicity is due to phosphine (hydrogen phosphide, phosphorus trihydride or PH_3) gas released instantly in the presence of moisture leading to multisystem involvement and serious consequences (8, 12, 17-19, 21-30).

Aluminum phosphide is available as tablets, pellets, granules or dust and contains phosphide in combination with other material such as ammonium carbonate. It may be synthesized as dark gray or dark yellow crystals, as well (8, 31-33). The brand names of ALP include Celphos, Alphos, Quickphos, Phosfume, Phostoxin, Gastoxin, Detia, Rotox, Fumitoxin, Talunex, Degesch, Synfume, Chemfume, Phostek, and Delicia (8, 34, 35). Due to the presence of substituted phosphines and diphosphines and on contact to the air, phosphine gas has a foul odor like decaying fish or garlic but is naturally colorless (8, 36, 37).

ALP may cause acute poisoning by either direct ingestion of the salts or indirect inhalation of the phosphine generated during its application (36). These days, ALP poisoning is common due to suicidal attempts in the agricultural societies such as Iran and Northern India (37). ALP is now easily available to commit suicide (38, 39). Unfortunately, it is quickly becoming a commonly used agent for suicide in Iran (8, 29, 40-45). The retrospective 5 and 10-year studies of acute poisoning cases at the department of India medical science shows a total of 279 and 623 cases of acute poisoning, of which, 37 (13.2%) and 138 (31%) were due to ALP poisoning (27). *In-vitro* and *in-vivo* studies have proved that its toxic effects are basically because of inhibition of cytochrome oxidase, the terminal enzyme of mitochondrial electron transport chain causing the generation of superoxide radicals and cellular peroxides and consecutive cellular injury by lipid peroxidation and other oxidant mechanisms (8, 23, 46-49). Aluminum phosphide insecticide and rodenticide is highly toxic to pests penetrating treated material and burrowing rodents (11, 50, 51). Studies conducted in the years as early as 1829 have reported the toxicity of phosphine in both humans and animals (14, 16-19, 21, 23-25, 50). Acute, subchronic, developmental, and cytogenetic studies have recently been indicated that the primary risk of exposure to phosphine is lethality (50, 52-56). Phosphine gas is also used in the synthesis of organophosphates and as a dopant in semiconductor production (50). Interestingly, as a result of its indoor

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application, its use is not expected to have any implications on animal species (57).
Effective antidote are lacking for this fumigant as one of the most toxic pesticides in the world. Also it causes many deaths in developing countries (58-60). We evaluated the effect of ALP on animals with the concept that it may help finding substituted treatment modalities for ALP poisoning in human cases.
We looked up the terms aluminum phosphide, phosphine, phostoxin, rice tablet, ALP , PH3, rat, rabbit, and animal in bibliographical databases such as the Tehran university of medical science (TUMS) digital library, Pubmed central, Scopus, Google Scholar, and British library. This review includes relevant articles published between 1962 and 2014.

2. Mechanism of Action:
The exact mechanisms of phosphine action remains unclear to date (61). However, some studies on different animals showed that PH3 induced lipid peroxidation and deoxyribonucleic acid (DNA) oxidation both *in vitro* and *in vivo* (62-64). Phosphine is a mitochondrial toxin that inhibits cellular respiration and induces oxidative stress in insects and mammalian cells (65, 66). In addition, a preliminary study proves that ALP poisoning can cause inhibit cholinesterase (67). On the other hand, the fumigant phosphine can disrupt mitochondrial function in the nematodes, insects, and animals such as rats at toxicologically concentrations (10, 68, 69). Nath *et al* showed that acetylcholine signaling is an important component of phosphine toxicity (10). A reduction in the activity of glutathione reductase was also observed in the study performed by Raina and Gill, while, no change was seen in the activity of glutathione peroxidase following aluminum phosphide administration (14). Also, an increase in chromosomal aberrations (CAs) and micronucleus (MN) assay rates as well as alterations in total antioxidant capacity (TAC) and total oxidative status (TOS) levels are seen due to ALP poisoning (70). Even more, it has been shown that genotoxicity and cytotoxicity are associated with oxidative stress because of increased reactive oxygen species (ROS) level (71).
The role of glutathione (GSH) in phosphine-induced oxidative toxicity is controversial. GSH levels in several tested tissues were reduced in aluminum phosphide-poisoned rats and humans, while the levels remained unchanged in insects and mammalian cells (65). Also, some studies demonstrated the inhibition of cytochrome oxidase (14, 16, 23, 70); catalase (14, 65, 72) and peroxidase (14, 65) while stimulating the production of hydrogen peroxide and increasing superoxide dismutase (SOD) and malondialdehyde (MDA) (65, 73).

3. Toxicokinetics:
Death is the main danger of phosphine exposures (6). Also, phosphine toxicity has seriously increased by repeated treatments using a sub-lethal dose of the fumigant (72, 74). Similarities have been indicated between phosphine toxicity and iron overload. It has been shown that phosphine could trigger iron release from storage proteins, increase lipid peroxidation and lead to cell injury and/or cell death (61). Some surveys demonstrated the role of GSH in modulating the PH3-induced oxidative damage in rat lung, kidney, and heart tissue evident by a significant increase in lipid peroxidation (16, 65). Also, some studies showed that PH3 induced lipid peroxidation and DNA oxidation in rat brain both *in vitro* and *in-vivo*(14, 69). Studies show that phostoxin treatment causes a decrease in Na^{+}- K^{+} adenosine triphosphatase (ATPase) activities in liver, kidney, and cardiac tissues as well as Ca^{++}- and Mg^{++} ATPase activities in liver (75). However, Dua and colleagues proved a reduction of glucose-6 phosphate dehydrogenaseactivity in their study (20).

4. Environmental Effects on Fumigation Success:

For successful eradication of the pests, fumigation should be done as soon as possible and simultaneously in each specific region (2). There are several factors to consider including burrow temperature, humidity, length and configuration, soil porosity, wind speed and direction and specific behavioral characteristics of the different species (76). Field trials suggest that the successful use of phostoxin tablets depends on a sufficient concentration of gas reaching the pest and soil moisture. Therefore, it may not be effective in the dry summer months (77-80). Choosing certain periods of the year (midsummer to late autumn) with careful application is a very important factor to increase the efficacy (78-81). The colony must be fairly-air tight, as well (15). Beerwinkle and Devaney suggested environmental temperatures above 15°C and relative humidity above 50% for complete decomposition of phosphine pellets (12). Interestingly, Nayak and Collins showed that at any concentration of phosphine, a combination of higher temperature and lower humidity made the fumigation period shorter (82).

5. Using ALP as an Insecticide:

Efficacy of ALP as a pesticide for killing animals like rats, rabbits, moles (83), mice, dogs, and squirrels has been proved in several studies. Human beings use this fumigant as an insecticide in grain-stored products because of its toxic effects on virtually all stages of insects commonly found in stored feeds (58). Among different insecticides, ALP is the most effective and the best results were given by using it to kill insect pests like *Red Palm Weevil*, *Rhynchophorus Ferrugineus L* (84-86), live-wood tea termites (15), and wood-destroying insects, *L. Africanus*(4). Hessian Fly (*Diptera: Cecidomyiidae*) (80) and Australian feral bees-Apismellifera

Table1: New treatment strategies for ALP poisoning in animals

Authors	Type of study	New treatment	effects	conclusion
Moghadamnia *et al*, 2000	Experimental (rats)	Na selenite 3 mg/kg	Improved pathological findings in lung and liver of the rats but no effect on survival rate	Na selenite improves pathological findings in lung and liver of the rats but no effect on survival rate
		*NAC 50 and 100 mg/kg	Decreased liver complications and increased survival rate	Immediately use NAC and vitamin C after ALP poisoning to increase the survival rate
		vitamin C 500-1000 mg/kg	Increased survival rate	Immediately use NAC and vitamin C after ALP poisoning to increase the survival rate
		Magnesium sulfate 3 mg/kg	No effect on survival rate	Magnesium sulfate did not improve the survival time and more studies need to examine pathological findings
Hsu *et al*, 2000	Experimental (rats)	Melatonin (10/kg), vitamin C (30 mg/kg), and beta-	PH3-induced changes were significantly or completely blocked by melatonin while	melatonin protects against oxidative damage in the brain, lung and liver of rats and suggests the involvement of

		carotene (6mg/kg)	vitamin C and beta-carotene were less effective or inactive.	reactive oxygen species in the genotoxicity of PH3
Lall*et al*, 2000	Experimental (rats)	Methylene blue (MB) (0.1%, 1 mg/kg/5min, IV)	MB caused a significant fall in MDA and methemoglobin (MeHb) levels with increase in survival rate	MB acts as an exogenous electron carrier and accelerates NADPH- dependent methemoglobin reductase activity.
Azad *et al*, 2001	Experimental (rats)	NAC infusion (6.25 mg/kg/min IV for 30 minutes)	Significantly increased survival time, stabilization of blood pressure and heart rate, decreased MDA**level and increased GSH Px*** levels	NAC increased the survival time by reducing myocardial oxidative injury
		****L- NAME infusion (1 mg/kg/min iv for 60 min)	Significant rise in blood pressure but precipitated ECG abnormalities. Pre- and post-treatment of L-NAME neither improved the survival time nor the biochemical parameters	L-NAME showed no protective effects in rats exposed to ALP
Shivani M *et al*, 2001	Experimental (rats)	Atropine(1 mg kg-1, intra peritoneal) + pralidoxime (5 mg kg-1, intra peritoneal) administered five minutes after ALP exposure	Increase survival time. Plasma cholinesterase levels were inhibited in rats poisoned with ALP as compared to controls	Atropine and pralidoxime can increase survival time
Hsu *et al*, 2002	Experimental (rats)	melatonin (10 mg/kg I.P., 30 minutes before PH3	The antioxidant melatonin effectively prevents the damage caused by ALP	Melatonin is a potent scavenger of free radicals and stimulates other antioxidant activity. Additionally, it readily penetrates biological barriers and gains access to every subcellular compartment

		Melatonin (1.0 or 2.0 mM)	Increased survival time	Melatonin reversed the toxic effect of ALP, probably because of its free radical scavenging ability and antioxidant activity.
Saidi H *et al*, 2011	Experimental (rats)	hyperbaric oxygen	improved the survival time	Hyperbaric oxygen may improve the survival time of the intoxicated rats with ALP, but it may not decrease the mortality rate. It may also be effective in humans
Baeeri*et al*, 2013	Experimental (rats)	$^{25}Mg^{+2}$ -carrying nanoparticle + Na bicarbonate (4 mmol/kg,i.v)	Increased BP and HR, increased antioxidant power, Mg level in the plasma and the heart; reduced lipid peroxidation and ADP, ATP ratio	^{25}MgPMC16 at 0.25 LD_{50} + Na bicarbonate was the most effective combination.
Saidi and Shojaie, 2012	Experimental (rats)	Intragastric irrigation with sweet almond oil	Increased survival rate	Siginificant reduction in mortality
Turkez and Togar, 2012	Experimental (rats)	*****LNE (200 mg kg1 injected IP)	LNE suppressed the genetic damage by ALP to bone marrow cells in vivo and reduced ALP-caused oxidative damage.	The protective effect of LNE might be ascribable to its antioxidant and free radical scavenging properties.
Ibegbu *et al*, 2013	Experimental (rats)	Vitamin E	Reduced the toxic effect on the liver	Ability of vitamin E to ameliorate or inhibit the action of phostoxin could be due to removing the ROS via very rapid electron transfer chain that inhibited lipid peroxidation
Baghaei *et al*, 2014	Experimental (rats)	******* IMOD	IMOD ameliorated the ALP- disturbed cardiovascular parameters such as bradycardia and hypotension	IMOD protects cardiovascular system, prevents oxidative stress and restores cellular ATP reserve
Kazemifar *et al*, 2014	Experimental (rats)	******MTH	Increased the survival rate and histopathological changes in kidney and liver	MTH may be beneficial in the treatment of acute ALP poisoning in rats in terms of survival rate and histopathologic changes in kidney and liver

*NAC: N-Acetylcysteine; **MDA: Malonyldialdehyde; ***GSH Px: Glutathione peroxidase; ****L-NAME: N-omega-nitro-L-arginine methyl ester; *****LNE: Laurusnobilis (L) leaf extract; ****** MTH: Mild therapeutic hypothermia; *******IMOD: Multi-Herbal Formulation

(87)-colonies were killed by fumigation with phosphine gas. The coffee berry borer-hypothenemus hampie (ferr)-can be well disinfected by fumigation with ALP (88). Palm dates are an important crop in several countries and ALP as an alternative to methyl bromide has been used successfully to control carob moth, Ectomyelois ceratoniae (zeller) (89, 90). To control psocid Liposcelisbostrychophila Badonnel as a widespread significant insect pest (Psocoptera: Liposcelidae) at any concentration of phosphine, a combination of higher temperature and lower humidity provides the shortest fumigation period (82). To fumigate sitophilus zeamais motsch (coleoptera, curculionidae), high concentrations of PH3 paralyzed the insect and decreased the respiratory rate (17). Studies show the effect of PH3 fumigation on sitophilusoryzae (L), as well (91, 92). Tribolium castaneum (herbst) (72), oryzaephilus surinamensis (L), lasioderma serricorne (f.) eggs of plodiainter punctella (hűbner), Cadracautella (Walker) (5), and red flour beetles, T. castaneum (1) are the other insects controlled with this fumigant. The mechanisms of toxicity and resistance are not clearly understood; some studies used the model organism, Caenorhabditis elegans to investigate the effects of phosphine on its proposed in-vivo target, mitochondria (61, 68, 93).

6. Dose Toxicity:

Pant and Tripathi showed that ALP killed *L. Africanus* larvae completely at 0.2% concentration (4). Dose of 40 mg/kg body weight was considered as the lethal dose 50% (LD50) in Moghadamnia and coworkers' study. Mice affected by the dosedied within 15-35 minutes (94). In another study, with a high-dose phosphine gas (40 mg) there was no recovery in blood pressure (BP), while the initial fall continued till all the animals died (95). Administration of 2 mg/kg of intraperitoneal phosphine induced lipid peroxidation in rat brain within 15 minutes (96).

Rat oral LD50 has been estimated to be 14 mg/kg; sub-chronic exposure of mice (4.5 PPM for 13 weeks) demonstrates significant increase in micronucleus frequency in bone marrow and spleen lymphocytes, as well (97).

According to a study done in 2011, oral LD50 of ALP in male rats was calculated to be 11.59 mg/kg.Initially, 15 mg/kg body weight of ALP was gavaged and resulted in 100% mortality, while after reducing the dose to 8 mg/kg, no mortality was seen. Thus, doses ranging between 8 and 15 mg/kg were applied while other variables were kept constant (98).

Muthu and associates proved that the LD50 values of PH3 ranged from 0.22 mg.hr /L (27°C) to 0.26 mg.hr/L (26.1°C) with related exposure periods of 5.2 to 7.4 hours, respectively, while it was 0.42 and 0.49 mg.hr /L with exposure periods of 6.2 and 8.8 hours, respectively (25). Another study demonstrated that the LD50 value of phostoxin was 2.20 mg/L for 96h of exposure (99).

7. Organ Toxicity:

Hemodynamic and cardiaceffects.ALP caused considerable tachycardia, hypotension, electrocardiogram (ECG) abnormalities, and finally, marked bradycardia (73, 95). It has been indicated that after ALP administration, BP and heart rate (HR) decrease while R-R duration increase (98). Also, in some studies performed on animals including rats and rabbits, significant reduction of hematocrit, platelet count, red blood cell count, and hemoglobin concentration of phostoxin-treated animals was shown (52, 75). There was a 5% decrease in erythrocytes, hemoglobin, and hematocrit in one group of a study after 13 weeks of exposure (52).

Neurotoxic effects.ALP exposure enhanced neuronal lipo-peroxidative damage with simultaneous changes in the antioxidant defense status in some studies, having serious effects on the function and structure of the central nervous system (14, 62). Another study on rats proved no

phosphine-related changes in the functional observational battery, motor activity, or neuropathologic assessments (50). Also, there was a significant decrease in all cytochromes in brain except cytochrome b, the levels of which remained unchanged (100).

Renal effects. An increase in serum blood urea nitrogen has been detected showing renal injury (74). In a study by Newton *et al*, kidney weights increased and coagulative necrosis of the tubular epithelium in the outer cortex was seen in some rats with intensive effects in females compared to males (52). In addition, in another investigation on rabbits, the phostoxin-intoxicated animals manifested degenerative changes in their kidneys (75). It has been suggested that PH3-caused oxidative stress might be related to its nephrotoxic effects (65).

Liver effects. Significant decrease in peroxidation of unsaturated fatty acids and the activity of cytochrome oxidase was seen (66%) which suggested that there was a decrease in the catalytic efficiency of the active oxidase molecules on ALP-treated animals (23). Phosphine inhalation caused a significant decrease in GSH concentration as well as 19–25% elevation in lipid peroxidation and 39% increase of 8-hydroxydeoxy guanosin in DNA of the liver (96). There was a notable dose-related increase in the activity of serum alkaline-phosphatase (ALP) in rats after subchronic exposure to phosphine (74) and phosphine toxicity inhibited respiration in rat liver mitochondria (65).

Significant biologically relevant increases in serum activity of alanine aminotransferase (ALT) and sorbitol dehydrogenase were observed at 10-PPM ALP exposure. All mice were killed after three exposures to 10 PPM of ALP and half of them had minimal to mild sub-capsular foci of hemorrhage and necrosis in the liver tissue (56). It has been proved that ALP induces cellular energy deficit which leads to compromised energy status of liver and brain coupled with significant changes in glucose homeostasis (20).

8. Uncommon features:

Food absorption, body weight gain, food and protein efficiency ratio, nitrogen absorption, biological value, net protein use and dry matter digestibility decreased in rats exposed to ALP (101). Ataxia, nervousness, anemia, and infections of varying severity were observed in another study (26). In another study on horses, clinical findings including profuse sweating, tachycardia, tachypnea, pyrexia, ataxia, seizures, and widespread muscle tremors were detected (58). ALP was found to induce genotoxic damage in the rat bone marrow cells (70).

In some studies (26, 55, 102), comparison between control and treated animals did not show any particular effect of phosphine at first, but did with passing time indicating a certain degree of aging in the animals. Rate of tumor development did not prove any toxic effects in phostoxin-treated animals (55). It is supposed that exposure to 5 PPM of PH3 by inhalation does not induce significant lethality in male mouse germ cells (54). Also, in another study after 15-PPM exposure, the animals just appeared lethargic and their breathing was shallow (55).

Horses affected by ALP experienced hypoglycemia (22 mg of glucose/dL of serum; reference limits, 58 to 134 mg/dL) and high serum lactate concentration (> 150 mg/dL; reference limits, 0.36 to 18.4 mg/dL) (58). The pathological findings included ecchymotic hemorrhages on the parietal pleura, pulmonary edema, hepatic lipidosis, hyperemia of the gastrointestinal mucosa, and lung, kidney, and spleen congestion. It is believed that inhibitory effects of ALP on cellular respiration and possibly lipoperoxidative damage due to an increase in the generation of oxygen free radicals leads to these abnormalities (58, 103, 104).

9. Dangers of use of fumigants:

Williams and Corrigan believe fumigants are commonly useless due to difficulty in

locating the material to animal burrows, open and well-ventilated structure, and complexity of burrows (51). On the other hand, it seems that fumigation is much more expensive than baiting or other ways for killing pests (105); when the material is placed in the animals' deep burrows, fumigation has the greatest effectiveness in spite of placing in the surface of the runways (106). Some researchers do not recommend fumigation as the first step to control large numbers of prairie dogs because it is expensive, time-consuming, and usually more dangerous to desirable wildlife species than toxic baits (107). It has been shown that ALP is not very successful in controlling pocket gophers because either gophers sense the poisonous gas and plug the tunnel or the fumigants diffuse into the soil, especially when it is dry (108).

10. Toxicity Management:

In a study by Moghadamnia and colleagues, male siri albino rats were used to show the effects of different treatments on ALP-poisoned rats. Sodium selenite had no effect on mortality rate and time of death; but, it would improve the pathologic findings such as lung and liver complications. N-acetylcysteine (NAC) delayed death and caused a definite improvement in liver complications. On the other hand, vitamin C delayed death while magnesium sulfate did not change the survival rate in ALP-poisoned rats. It is therefore recommended that NAC and vitamin C are immediately initiated after ALP poisoning and subsequent liver functional and biochemical tests are performed afterwards (94).

Several researches have shown that a high basal phosphatidyl ethanolamine plasmalogen (PlsEtn) or the capacity to synthesize new ethanolamine lipids (particularly PlsEtn) may protect against PH3 toxicity (62). This is while some results demonstrate that endogenous GSH has a key role in protecting against PH3-induced lipid peroxidation in rat lungs (64, 65).

Hsu and associates examined phosphine toxicity and protective effect of melatonin on male Wistar rats (with mean weight of 250±30 g). The effects of PH3 on GSH and GSH disulfide (GSSG) levels are closely paralleled by the increase in lipid peroxidation of brain (42%), lung (32%), and liver (25%) and melatonin, vitamin C, and beta-carotene abolished these effects. In conclusion, the antioxidants reduce PH3-induced oxidative damage with an effectiveness order of melatonin> vitamin C ≥ beta-carotene (96).

On an overall basis, the most effective antioxidant-melatonin-limits GSH depletion, GSSG formation, lipid peroxidation, and 8-OH-dGuo formation in phosphine-treated rats tissues (60, 64, 109-113). Male Wistar rats weighting 250±30 g were used to evaluate oxidative toxicity of phosphine in kidney and heart in another study. Melatonin was used because of its potency as scavenger of free radicals and stimulant of other antioxidant activity (65, 114) . It also penetrates biological barriers and gains access to every subcellular compartment (65, 115) .

A preliminary study on rats found that cholinesterase inhibition caused by ALP poisoning responded to treatment with atropine and pralidoxime (PAM). In the abovementioned research, 45 Wistar rats were divided into three groups. Fifteen rats were treated with atropine (1mg/kg) and PAM (5mg/kg) intraperitoneally five minutes after intragastric administration of ALP. Atropine and PAM treatment increased the survival time in 9 out of 15 rats and resulted in complete improvement in the remainder. Also, plasma cholinesterase levels were inhibited in ALP-treated animals as compared to the control group (27). Additionally, the muscarinic acetylcholine antagonist-atropine-protects rats against phosphine exposure suggesting acetylcholine signaling (as a regulator of the parasympathetic nervous system in mammals and an activator of the metabolic pathways) is an key role of phosphine toxicity (27, 67). To improve the survival

rate, we can apply oral sweet almond oil, especially immediately after poisoning with ALP. Adult Wistar rats (n=35) weighing 200 to 250 g were divided into four groups. Group 3 and 4 were treated with sweet almond oil immediately and 30 minutes after ALP ingestion, respectively; the results demonstrated that intragastric sweet almond oil could increase survival time of animals exposed to ALP (110).

Hyperbaric oxygenation (HBO) may not decrease the mortality rate but may probably improve the survival time of the intoxicated rats with ALP. To prove this, Wistar rats with weighting 150 to 250 g were examined by Saidi and colleagues. Their results revealed that HBO therapy might increase survival in ALP-intoxicated rats; but, there was no significant difference between pure O2 and compressed air. In addition, after HBO treatment process, a higher mortality rate in ALP toxicity compared to other intoxications indicates that the mechanism of action of ALP may be more complex that just simply inhibiting cytochrome oxidase (116).

Interestingly, NAC increases the survival time by reducing myocardial oxidative injury whereas N-omega-nitro-L-arginine methyl ester (L-NAME) has shown no such protective effects. The rats (200-250 g) were examined to investigate the protective effects of NAC and L-NAME in ALP poisoning. ALP toxicity induced significant hemodynamic and biochemical changes which decreased the survival rate. NAC infusion (6.25 mg/kg/min IV for 30 minutes) caused no important hemodynamic and biochemical changes; but, pre-and post-treatment with NAC increased the survival time, stabilized BP, HR, and ECG. Decreased MDA and increased glutathione peroxidase (GSH px) level compared to ALP group was observed (73).

Infusion of L- NAME (1mg/kg/min IV for 60 minutes) caused significant rise in BP, but precipitated ECG abnormalities (114, 117). Pre- and post-treatments with L-NAME did not improve the survival time and the biochemical parameters despite significant rise in BP. Co-administration of both drugs worsened hemodynamic and biochemical parameters and reduced survival time (73). Other researchers observed that Laurusnobilis (L) leaf extract (LNE) suppressed ALP-induced genetic damage to bone marrow cells in male eight-week-old Sprague–Dawley rats weighing 180 to200 g. Interestingly, LNE strongly reduced ALP-induced oxidative stress. The plant, thereby, was introduced as a prospective source of natural metabolites which could be precursors of effective, preventive, or protective treatments against ALP toxicity (70).

In a study on cardiovascular toxicity of ALP, magnetic magnesium nano-carrier (25 Mg PMC16) improved ALP-induced toxicity and cardiac failure. A total of 54 male Wistar rats weighing 200 to250 g were used in this study. The results showed that oral LD50 of ALP in male rats was 11.59 mg/kg. Therefore, 0.25 of LD50 dose of ALP was used as the test dose in the study. It was revealed that 25MgPMC16 had a marked benefit in ALP toxicity by reducing the oxidative stress and increasing BP and HR (98).

Although there is not any specific antidote for phosphine toxicity, supportive care including frequent emesis during the early stages of the treatment increases the survival (58-60). The report on horses treated by gastric lavage and further nasogastric use of di-tri-octahedral smectite confirms this. In addition, supportive care including IV fluid administration maintains enough hydration and normal blood pressure. The IV administration of dextrose and corn syrup is used to maintain blood glucose concentrations within reference limits, as well. Phenobarbital (0.003 mg/kg in a 500-mL bolus of physiologic saline (0.9% NaCl) solution) was intravenously used to prevent seizures; atropine (0.01 to 0.07 mg/kg (IV) and 0.02 to 0.14 mg/kg (subcutaneous)), lactated ringer's solution (10 to 25 L, IV), and sedatives such as

xylazine (0.4 to 0.8 mg/kg, IV) have been administered to treat horses (58).

An experimental study on rats was done to evaluate if the survival rate and histopathology of liver and kidney improved after using mild therapeutic hypothermia (MTH). Male Sprague-Dawley rats were randomly divided into four groups. The first and the second group received only the vehicle of ALP and no drug, respectively. The third and the fourth groups were given ALP with LD50 dose. During the study (24 hours), the core body temperature of animals in the fourth group was kept in the 32 to 35 degrees centigrade range. Mean survival time in group 3 was 9.1 hours while it was 18.1 in group 4 (118).

Effects of vitamin E, as an antioxidant, on phostoxin-induced changes in the liver and haemato-biochemical parameters in Wistar rats were studied in 2013. Thirty adult Wistar rats with the average weight of 140 g of both genders were divided into six groups. Phostoxin was given through inhalation and oral vitamin E was administered at 800mg/kg body weight for animals in groups 2, 3 and 6. Body weight of the rats increased which could be due to increase in the rats' appetite. On the other hand, this study showed significant increases in biochemical parameters including aspartate transaminase (AST) and ALT levels in the serum of phostoxin-treated rats when compared to the controls. Vitamin E administration reduced the toxic effects on the liver which suggested the ability of vitamin E to ameliorate or inhibit the action of phostoxin (83). This effect could be because of removal of the ROS via very rapid electron transfer chain that inhibited lipid peroxidation (119, 120).

In a study on the rat model of ALP poisoning, the point was to investigate the oxygen free radical generation, methemoglobinemia and effect of methylene blue (MB) treatment on the survival time of those animals. Albino rats of either sex (150 to 200 g) were divided into two groups and ALP(50 mg/kg, intragastric) was used in one group while the other one received ALP+ methylene blue (0.1%, 1mg/kg/5min, IV). The results showed that MDA and methemoglobin (MeHb) levels increased during the study suggesting that methemoglobinemia could be due to increased oxygen free radicals. Methylene blue caused a significant fall in both parameters and increased survival rate. It probably acts as an exogenous electron carrier and accelerates nicotinamide adenine dinucleotide phosphate-oxidase (NADPH)- dependent methemoglobin reductase activity (121).

Positive role of IMOD (a multi-herbal formulation containing tanacetumvulgare, urticadioica and rosacanina extracts enriched by selenium, urea, and electromagnetic field) was proved in ALP-poisoned rats which could be due to protection of cardiovascular system, prevention of oxidative stress, and restoration of cellular ATP reserve. Fifty-four male Wistar rats weighing between 200 and 220 g were divided into nine groups and received IMOD at doses of 13, 20 and 30 mg/kg intraperitoneally 30 minutes after intragastric gavage of ALP (0.25 of LD50). ALP ingestion caused significant disturbance in cardiovascular system while using IMOD normalized these adverse effects (122).

11. Cautions:

ALP should be handled cautiously. Attention should be paid not use ALP in any situation that may expose people or domestic animals to the gases. Only licensed structural pest control operators should use ALP near buildings occupied by humans, livestock, or pets. Because of its inherent potential hazards (18, 123, 124), wearing cotton gloves and long-sleeved shirts during ALP administration is also warranted (125).

12. Conclusion:

Aluminum phosphide is a frequently used grain fumigant because of its highly potent characteristic, cost effectiveness, and easy availability. ALP also acts as an important rodenticide which affects the whole

environment directly and indirectly. Poisoning by phosphine rapidly disturb mitochondrial morphology, inhibit oxidative respiration, and cause a severe drop in mitochondrial membrane potential. This failure of cellular respiration is likely to be due to inhibition of cytochrome C oxidase activity. Phosphine can also form the highly reactive hydroxyl radical and inhibit both catalase and peroxidase leading to lipid peroxidation and reduce GSH which is one of the main antioxidant defenses.

Almost all the vital organs are affected in case of ALP poisoning. The mortality rate is very high because of a number of factors including lack of complete understanding of its kinetics and mechanism of action and, not to forget, a suitable antidote. A number of possible treatments have been tried or experimented with, but they all need further validation (Table 1). Meanwhile, preventive measures such as limited access to phosphide compounds, regulations to ban its use as a pesticide, and keeping health professionals abreast with the latest knowledge about early management of phosphide poisoning might help to control the risk of death due to this poisoning.

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